REMARKS

Claims 1-3, 6, 7, 10-12, 15-21, and 41 are pending in the application and under active consideration.

35 U.S.C. § 103

Claims 1-3, 6, 7, 10-12, 15-19, and 41 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over the reference of Gorczynski et al. (Cellular Immunol. (1995) 160:224-231; hereinafter "Gorczynski") in view of Nakai et al. (Blood (1998) 91:4600-4607; hereinafter "Nakai"), and further in view of Wakita et al. (J. Biol. Chem. (1998) 273:9001-9006; hereinafter "Wakita"). Gorczynski is cited for teaching the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of an animal. Nakai is cited for teaching a method for sustained expression of a gene in the liver of an animal using an adeno-associated viral particle that expresses human blood coagulation factor IX wherein the adeno-associated viral particle is delivered to the liver by portal vein injection. Wakita is cited for teaching that conditional transgene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of a trangenic mouse results in an animal that can be used as a tool to investigate the immune responses and pathogenesis of HCV infection.

In maintaining the rejection, the Final Office Action alleges that it would have been obvious to one of ordinary skill in the art to make an animal tolerant to an HCV gene by delivering an adeno-associated viral particle expressing HCV E1 or E2 to the liver of the animal by portal injection. The Final Office Action further asserts:

> One of ordinary skill in the art would have been motivated to combine the teachings based on the teachings of Wakita that an animal that expresses an HCV transgene in the liver of an animal results in an animal that is "a powerful tool with which to investigate the immunoresponses and pathogenesis of HCV infection" (see abstract of Wakita). Furthermore, it would have been recognized that portal injection of a vector that expresses a protein is an easier way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita. (Final Office Action, page 4.)

In addition, claims 1-3, 6, 7, 10-12, 15-21, and 41 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over the reference of Gorczynski et al. (*supra*) in view of Nakai et al. (*supra*), and further in view of Wakita et al. (*supra*) and further in view of Donnelly et al.

(WO 97/47358; hereinafter Donnelly). Gorczynski, Nakai and Wakita are applied as above. Donnelly is cited for allegedly teaching that a nucleic acid encoding HCV NS5a could be use used to raise an immunological response to HCV in an animal. (Final Office Action, page 6). Applicant respectfully traverses the rejections under 35 U.S.C. § 103 and the Office's purported facts underlying the rejections on the following grounds.

Gorczynski fails to describe sustaining the presence of antigen in the liver or successfully maintaining tolerance in an animal model for at least one month, as claimed. On the contrary, Gorczynski describes the injection of lymphoid or spleen cells into the portal veins of mice **a few days** before graft transplants to delay transplant rejection (see page 226, col. 2). All of the mice rejected their skin grafts within 22 days (see FIG. 2 at page 227). Therefore, **no long-term tolerance** to grafts was achieved. It is **not predictable** that tolerance to a particular immunogen can be achieved in an animal model for more than one month, as the Examiner maintains. Gorczynski fails to describe or suggest any animal model in which the presence of antigen was sustained for more than one month to achieve tolerance.

Furthermore, Gorczynski fails to describe anything pertaining to HCV. Gorczynski fails to describe or suggest any method for achieving sustained expression of an HCV **protein** in the liver for at least one month. Rather, the focus of Gorczynski is on methods of delaying transplant rejection of skin allografts by injection of lymphoid or spleen **cells** into the portal vein of an animal. Applicant reiterates that transplant rejection still occurred within **less than one month**. Thus, Gorczynski fails to disclose or suggest any method for preparing a stable animal model of immunological tolerance for screening agents that modulate tolerance to HCV.

Nakai fails to demonstrate that expression of HCV immunogens can be sustained in the liver for at least one month. Although Nakai teaches the sustained expression of Factor IX in the liver, the presumption that methods of expressing Factor IX are necessarily applicable to HCV genes is unsupported. It is **not predictable** that a particular gene can be expressed at sufficient levels under the same conditions as another completely unrelated gene, as the Examiner maintains. Furthermore, the subject matter of Nakai is not analogous to the pending case. Nakai describes methods of gene therapy for the purpose of treating hemophilia B by expressing Factor IX in the liver. Nakai fails to describe methods for expressing genes, in general, at sufficient levels and for sufficient periods of time in order to produce immunological tolerance in an

animal. Applicant again emphasizes that human Factor IX is **not an immunogen**, but rather, an **endogenous protein normally synthesized in the liver** (see, *e.g.*, page 4600, first column). Therefore, human Factor IX would not be expected to produce an immune response and cannot be used to produce an animal model of immunological tolerance. Moreover, since Factor IX is normally produced in the liver, there would be a presumption of success in expressing Factor IX in the liver that cannot be extrapolated to other genes not normally expressed there. Nakai fails to teach or suggest any method for inducing tolerance to antigens in an animal model, as claimed.

In referring to the transgenic mouse taught by Wakita as a "powerful tool with which to investigate the immune responses and pathogenesis of HCV infection," which supposedly provides the motivation to combine the references (Final Office Action, pages 4 and 13), the Examiner completely misrepresents the teachings of Wakita. Wakita fails to even mention immunological tolerance, nor using the transgenic mouse as a model of tolerance. The general references to immune responses and pathogenesis in Wakita fail to specifically address immunological tolerance. As defined in the instant application, ""tolerance" or "tolerant" refers to an immunological state in which the effector cells of the immune system **do not respond** to an immunogen and **do not become activated** upon contact with the immunogen" (see page 5, lines 21-23, emphasis added). Wakita, on the contrary, describes Cre/loxP-mediated conditional expression of HCV proteins in transgenic mice in which the Cre/loxP system is used to control expression of HCV transgenes such that the antigens are produced only transiently in order to generate **an antibody response** (see page 9006, col. 1). Thus, Wakita can be described as teaching away from the claimed invention, because the expression of the antigens is intentionally kept transient in order to retain immune responsiveness to the HCV antigens. Wakita fails to describe or suggest sustained expression of HCV antigens for at least one month in order to achieve immunological tolerance, as claimed. Thus, the reference to the transgenic model of Wakita as "a powerful tool" has nothing to do with methods of studying immunological tolerance.

Furthermore, Wakita does not suggest any non-germline animal model as in the instant case. Applicant reiterates that transgenic animals are usually less desirable as models of tolerance because of the presence of antigens at birth, albeit in the transgenic model of Wakita,

the HCV genes are switched off. Moreover, the use of a transgenic mouse, expressing HCV structural proteins, by Wakita does not automatically suggest an animal model of tolerance, let alone an animal model for screening agents that modulate tolerance, as described in the instant application. Wakita fails to even mention immunological tolerance, nor using the transgenic mouse in this manner as a model of tolerance.

There is nothing in the secondary reference of Donnelly to cure the deficiencies of Gorczynski, Nakai, and Wakita. Donnelly has nothing to do with immunological tolerance, but rather, pertains to vaccines that generate an immune response to HCV. Donnelly describes intramuscular injection of polynucleotides encoding HCV antigens to generate antibody and CTL immune responses against HCV. See, *e.g.*, page 5, lines 25-27 and page 11, lines 29-33. Donnelly fails to teach or suggest anything regarding nucleic acid immunization by injection in the portal vein, or sustained expression of antigens in the liver to achieve immunological tolerance. Thus, the cited combination fails to disclose or suggest the methods as claimed.

The recent decision by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 (U.S. Apr. 30, 2007) reaffirmed the viability of the four factual inquiries underlying an obviousness analysis provided in *Graham v. John Deere*, 148 USPQ 459, 467 (U.S. 1966). These factors include: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary considerations. Moreover, the Supreme Court in *KSR* recognized that the "teaching, suggestion, or motivation" analysis provides a helpful insight in determining whether the claimed subject matter is obvious. This analysis is provided in MPEP 2142. In particular, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Both the teaching or suggestion to make the claimed combination, as well as the reasonable expectation of success, must be found in the prior art, not in applicant's disclosure. See, e.g., *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). Based on the foregoing, applicant respectfully submits the Office has failed to establish a *prima facie* case of obviousness.

The Office has failed to provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions." *KSR*, page 13. In fact, the evidence is to the contrary. The cited art fails to provide evidence that an animal model as claimed could be prepared successfully for screening for agents that modulate immunological tolerance to an HCV immunogen. The primary reference of Gorczynski fails to describe or suggest any method for achieving long-term immunological tolerance lasting for more than one month. On the contrary, the methods of Gorczynski delayed transplant rejection of skin allografts for less than one month; therefore, Gorczynski fails to provide any reasonable expectation of success that an animal model of immunological tolerance, as claimed, could be produced. Additionally, there can be no reasonable expectation of success that HCV antigens could be expressed at sufficient levels to invoke immunological tolerance based on the expression of a completely unrelated protein in the liver, as described by Nakai.

As explained above, Wakita teaches away from an animal model of immunological tolerance with sustained expression of an HCV immunogen. Wakita instead teaches an animal model in which the expression of antigens is intentionally kept transient in order to retain immune responsiveness (see, *e.g.*, page 9006, col. 1). Wakita explicitly states that the "advantage of this system is that the transgenic animal is immunocompetent for the transgene product, which is extremely useful for examining immunological reactions against transgene products such as infectious agents" (see page 9005, col. 1). Thus, the animal model of Wakita is described as a "powerful tool" for studying immune reactions, not tolerance.

Moreover, Donnelly pertains to vaccines that induce immune responses to HCV and has nothing to do with methods of generating immunological tolerance. Thus, no combination of the cited references teaches or suggests a method for producing an animal model for screening for agents that modulate tolerance to HCV immunogens, nor do the references provide a reasonable expectation of success that such an animal model of immunological tolerance, as claimed, could be produced.

For at least these reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicant submits that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicant invites the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

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